Regions/ORD Endocrine Disruptors Workshop (Atlanta GA May 1-3, 2001)

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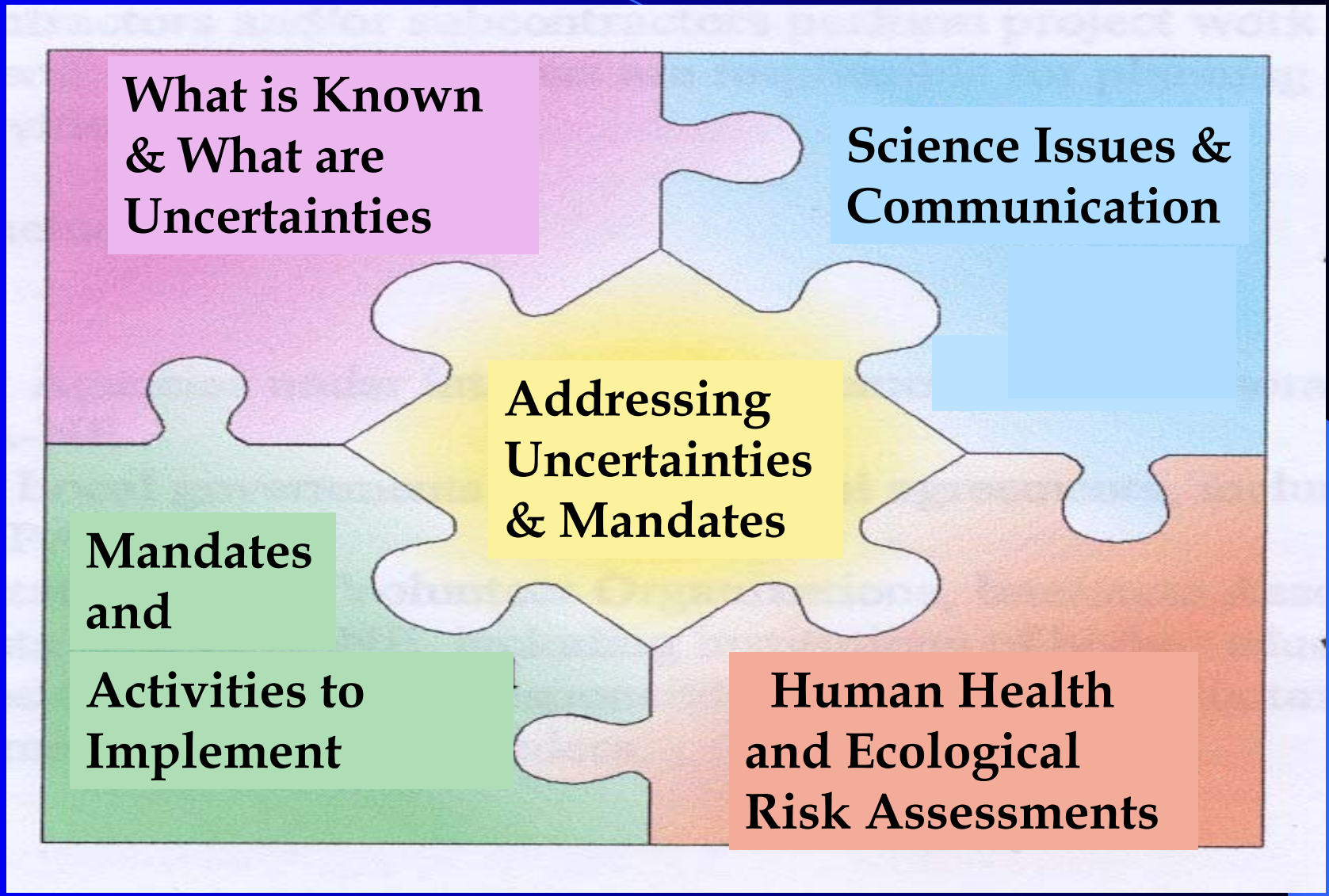
Reported to the National Risk Assessors Training and Conference

Bandera TX May 21-25, 2001

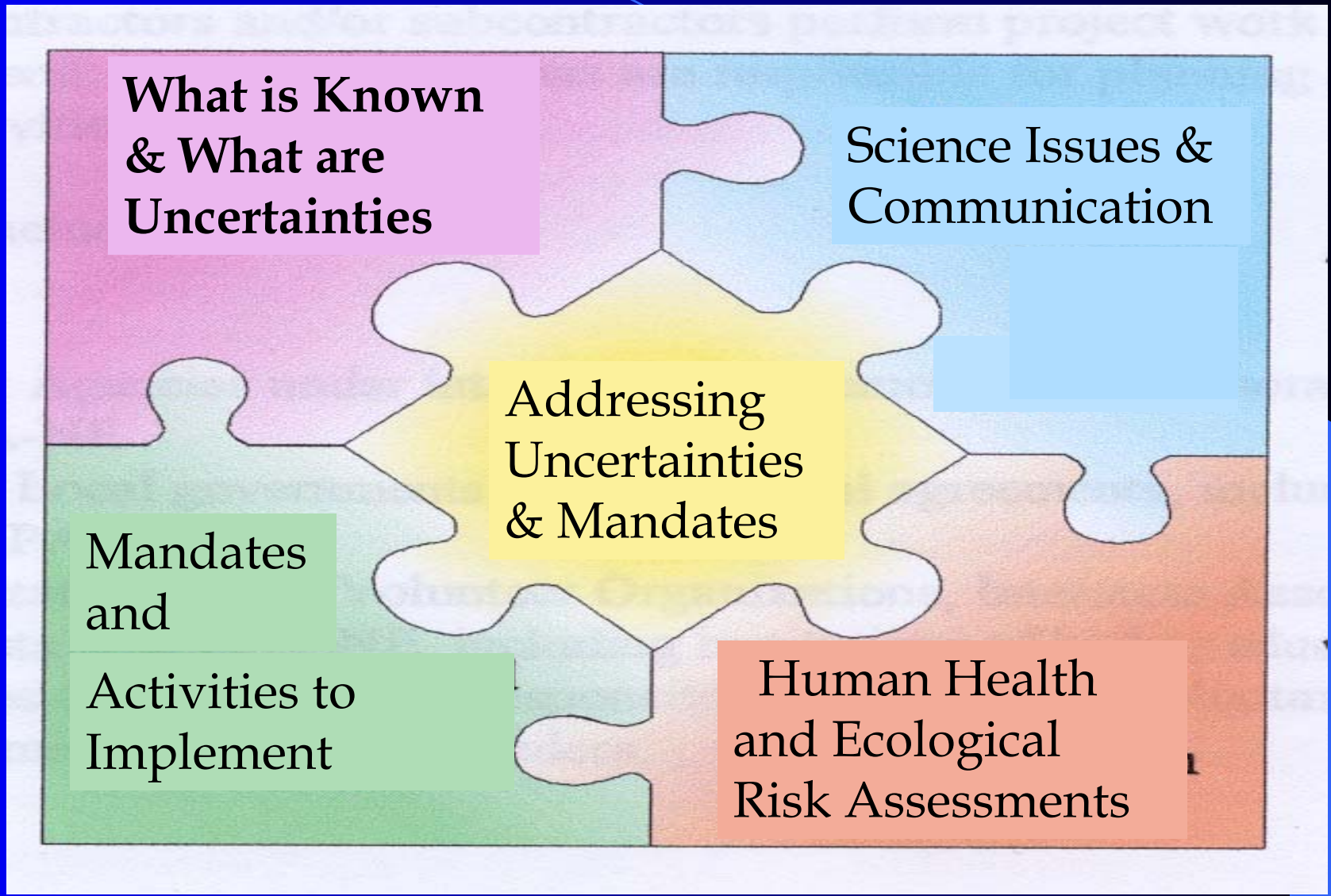
Outline Of Presentation

- **Endocrine Disruptor (ED) Workshop Themes**
- **Research (and Regulation) Past, Present and Future**
- **Three Things I Learned**
- **How To Get More Information**

Overview of ED Workshop Themes



ED Workshop Themes



What is an Endocrine Disruptor ?

"An exogenous agent that interferes with the *synthesis, secretion, transport, binding, action,* or *elimination of natural hormones* in the body that are responsible for the *maintenance of homeostasis, reproduction, development* and/or *behavior.*" Risk Assessment Forum EPA/630/R-96/012 February 1997

Classes of EDCs

Effluents	**BKME, STW**
Flame Retardants	**PBDEs**
Fungicides	**Vinclozolin**
Herbicides	**Atrazine**
Insecticides	**Methoxychlor**
Metals	**Tributyltin**
Pharmaceuticals	**Ethynyl Estradiol**
Phenols	**Bisphenol A**
Plasticizers	**Phthalates**
Polyaromatic Hydrocarbons	**PCBs, dioxin**
Soy Products	**Genistein**
Surfactants	**Alkylphenol Ethoxylates**

Science Policy Council Highlights / Major Conclusions

- There appears to be a common theme about endocrine disruption both in humans and wildlife.
- "With few exceptions (e.g., DES, dioxin, DDT/DDE) a causal relationship between exposure to an environmental agent and an adverse effect on human health operating via an endocrine disruption mechanism has not yet been established." Risk Assessment Forum EPA/630/R-96/012 February 1997

Major Conclusions

Female Reproductive Effects

- ***Endometriosis*: Etiology unknown, no known correlation with serum levels of halogenated aromatic hydrocarbons; recommend evaluating non-primate models**
- ***Breast Cancer*: No clear evidence for organochlorine pesticides, PCBs, dioxins; cannot assign a single cause; need more animal testing models**

Major Conclusions (Continued)

Male Reproductive Effects

- ***Decrease In Sperm Counts***: Still controversial; general widespread reduction not supported
- ***Testicular Cancer***: Evidence of an increase but cause unknown
- ***Prostate Cancer***: Cannot discount role of endocrine disruption; some correlation with herbicides and coke oven emissions

Major Conclusions (continued)

Hypothalamus and Pituitary

There is concern about exposure to EDs during development because many feedback mechanisms are not yet functional. Tests need to consider role of the brain and pituitary.

Thyroid

Many agents (e.g., urea derivatives, TCDD, polyhalogenated biphenyls) have been shown to effect hormone levels.

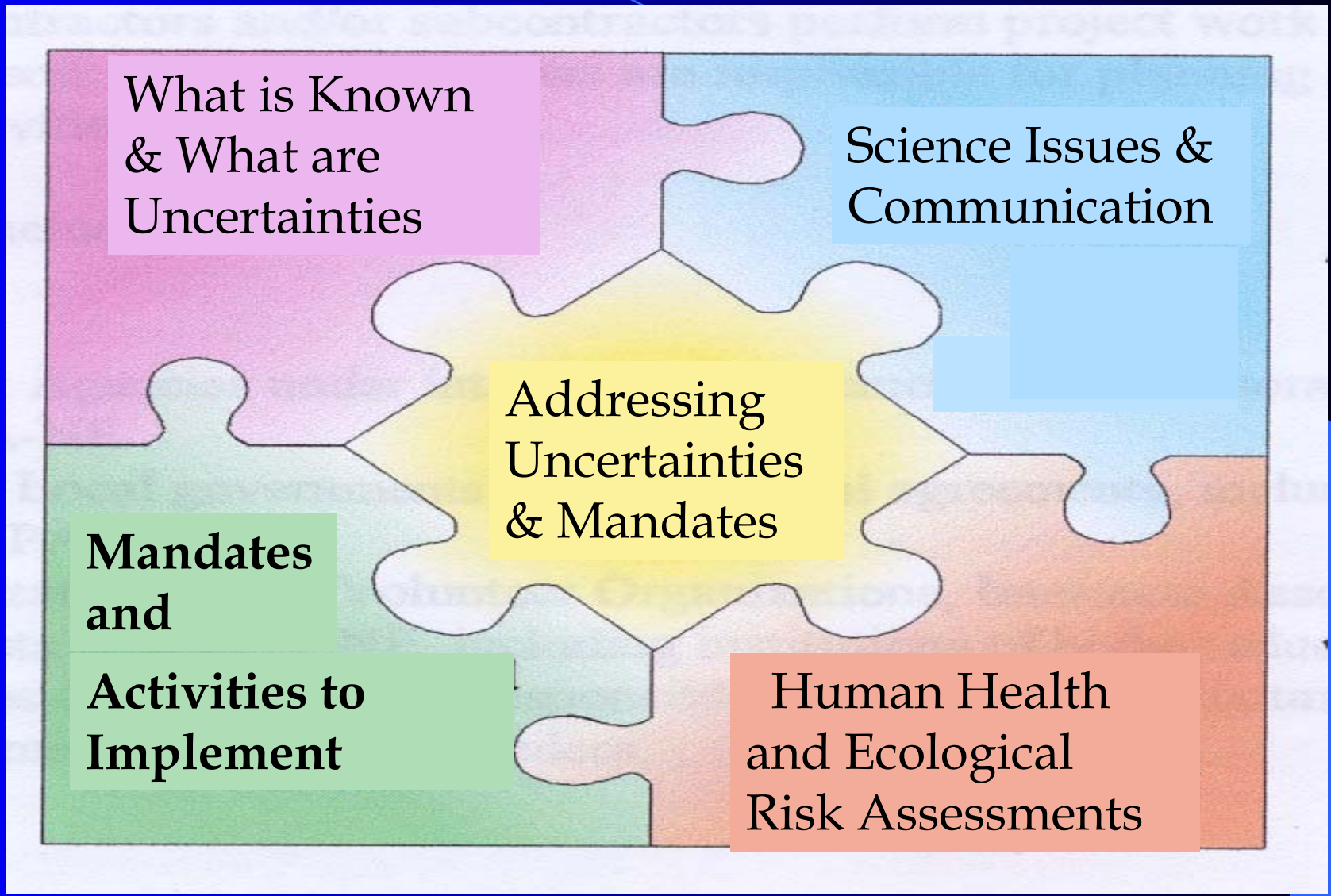
Major Conclusions (continued)
Human Health Effects

- The Science Policy Council Panel concluded "that exposure to a single xenoestrogenic compound, under current environmental conditions, is probably insufficient to evoke an adverse effect in adults." Risk Assessment Forum EPA/630/R-96/012 February 1997

Major Conclusions (continued)
Ecological Effects

- There are several well documented aquatic and wildlife ED effects:
  - TBT and Imposex/Intersex in gastropods
  - Phytoestrogens and masculinazation of fish
  - Feminization of male birds (gulls)
- Comparable ED effects data are lacking for many taxa, especially amphibians
- Need methods and longer term tests to determine ED effects at both the population and community levels

ED Workshop Themes



Science Policy Council's Interim Position

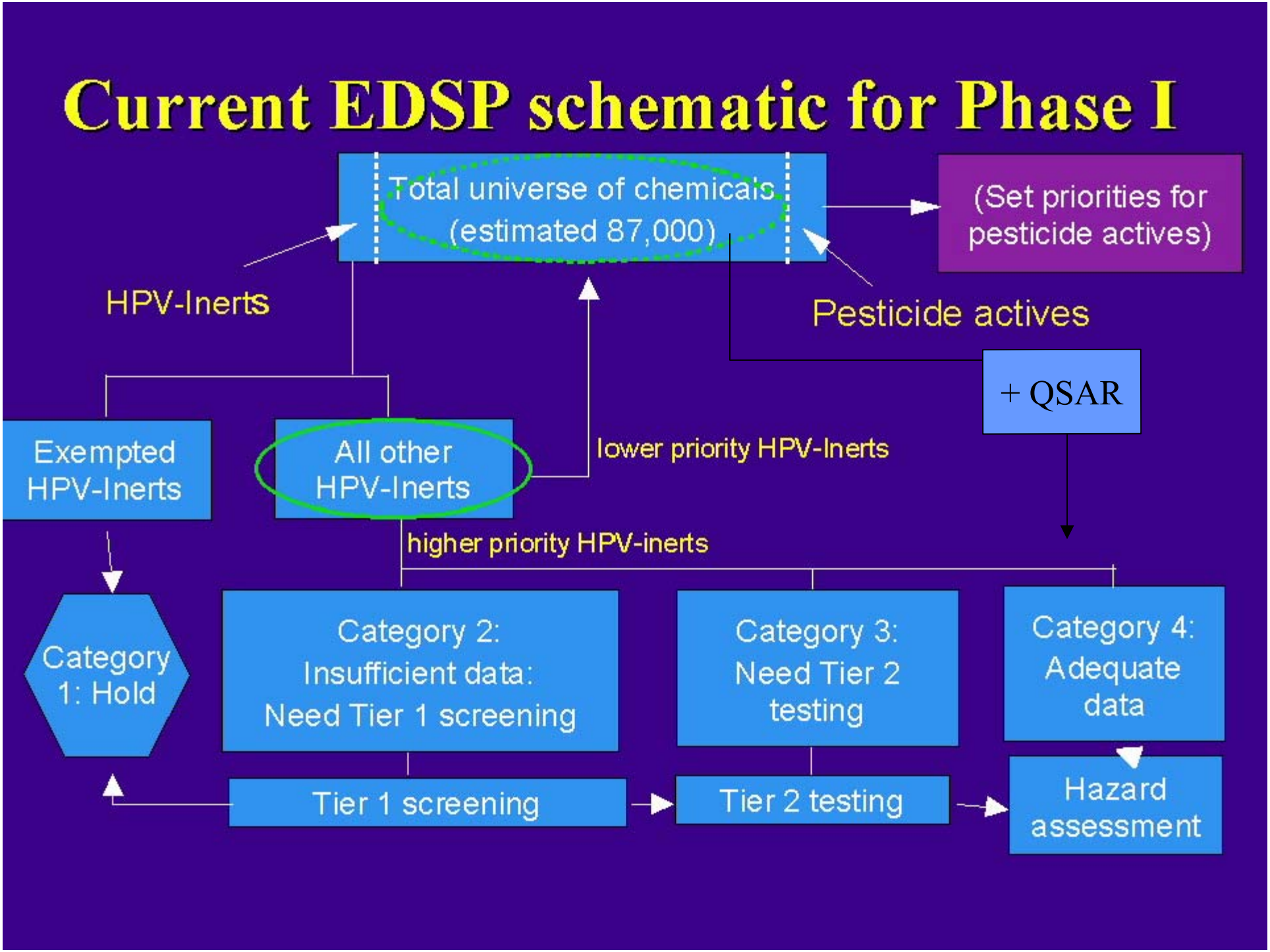
"*Based on the current state of the science, the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or mechanism of action potentially leading to other outcomes, for example carcinogenic, reproductive or developmental effects, …*" **Risk Assessment Forum EPA/630/R-96/012 February 1997**

This position could change as additional data become available.

OPPTS
Endocrine Disruptors Screening Program

IMPLEMENTATION DRIVERS

- FQPA (Food Quality Protection Act) mandates
- Conventional FIFRA/TSCA Authorities
- FY 2000 Report to Congress on EDSP
- Stakeholder input since 1996
- NRDC lawsuit and settlement agreement


Current EDSP schematic for Phase I
Total universe of chemicals
(estimated 87,000)
(Set priorities for pesticide actives)
HPV-Inerts
Pesticide actives
+ QSAR
Exempted HPV-Inerts
All other HPV-Inerts
lower priority HPV-Inerts
higher priority HPV-inerts
Category 1: Hold
Category 2: Insufficient data: Need Tier 1 screening
Category 3: Need Tier 2 testing
Category 4: Adequate data
Tier 1 screening
Tier 2 testing
Hazard assessment

ENDOCRINE DISRUPTOR PRIORITY SETTING DATABASE

- **Rank chemicals based on existing exposure and effects information and data**
  - **Exposure compartments: frequency of occurrence, concentration or quantity to rank chemicals**
  - **Effects compartments: LOAEL, NOAEL**
  - **Develop QSARs to assist chemical ranking**
  - **Rank chemicals on exposure and effects separately and combined**
- **Focus on commodity chemicals**

http://www.epa.gov/opptintr/chemrtk/volchall.htm

PRIORITY SETTING FOR PESTICIDES

- Sort and prioritize “other” (inert) ingredients using EDPSDB
- Run Pilot program for 25-50 (already-registered) active ingredients
- Develop criteria to examine existing data
- Utilize criteria, re-registration and tolerance reassessment schedules to set priorities

EDSTAC Tier 1 (screening) assays

- **Receptor binding assays (ER and AR)**
- **Uterotrophic**
- **Hershberger**
- **Pubertal female**
- **Steroidogenesis**
- **Frog metamorphosis**
- **Fish reproductive screen**

EDSTAC Tier 2 – Multi generation tests

- **Mammalian development and reproduction**
- **Avian development and reproduction**
- **Mysid shrimp life cycle**
- **Fish reproduction and development**
- **Amphibian development and reproduction**

Summary for EDSTAC

2000 2001 2002 2003 2004 2005

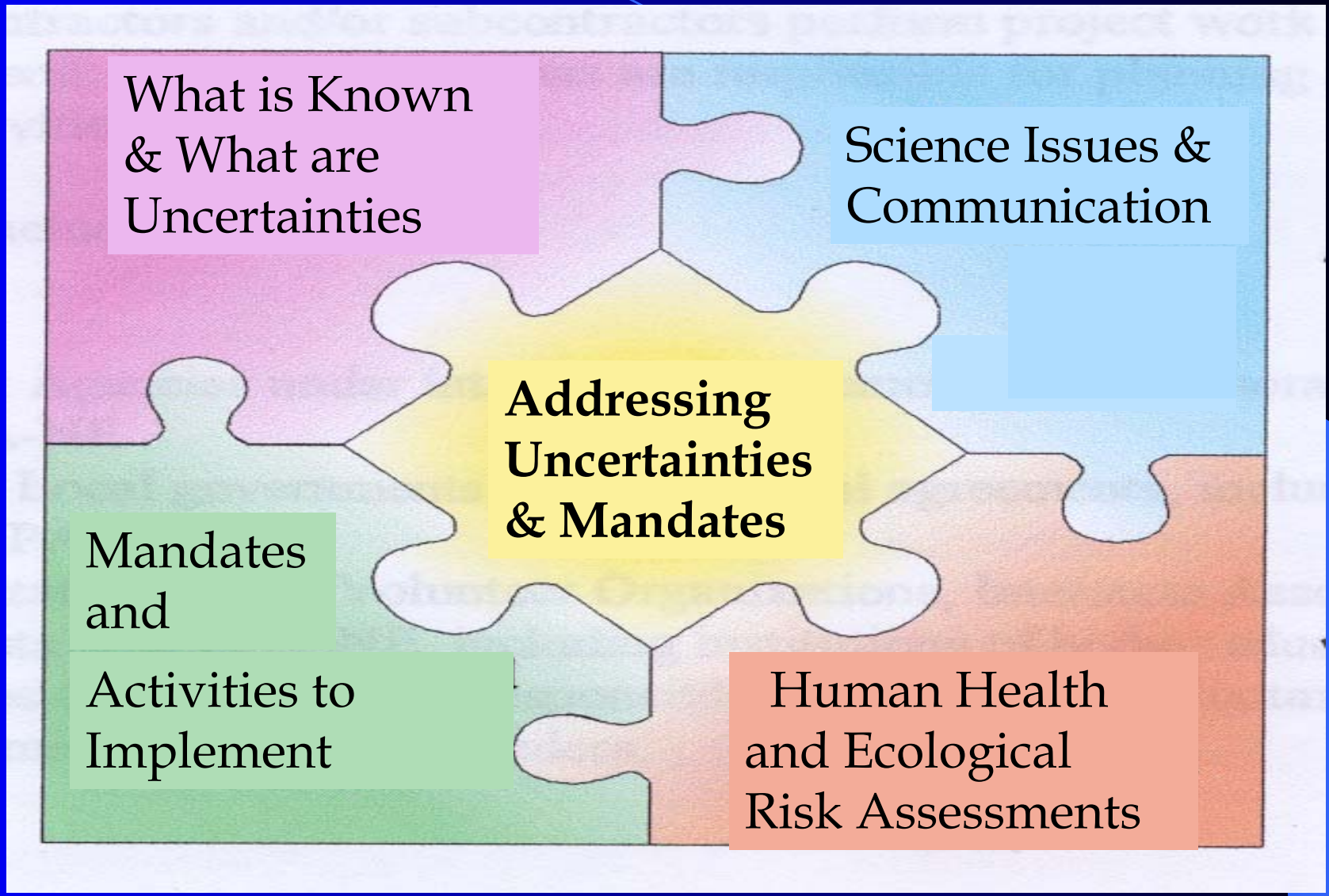
Priority Setting

Tier I Validation

Tier II Validation

Phase I Implementation

ED Workshop Themes



Major EDC Uncertainties

- **Exposure-Outcome Linkages**
  - **Latency**
  - **Persistent vs. non-persistent contaminants**
  - **Fate and transport**
  - **What effects are occurring in humans?**
- **Comparative toxicology**
  - **Sequence homology, binding, action**
- **Dose-response relationships**
  - **Shape, monotonicity**
  - **Interaction with “endogenous” diseases**
  - **Testing protocols**

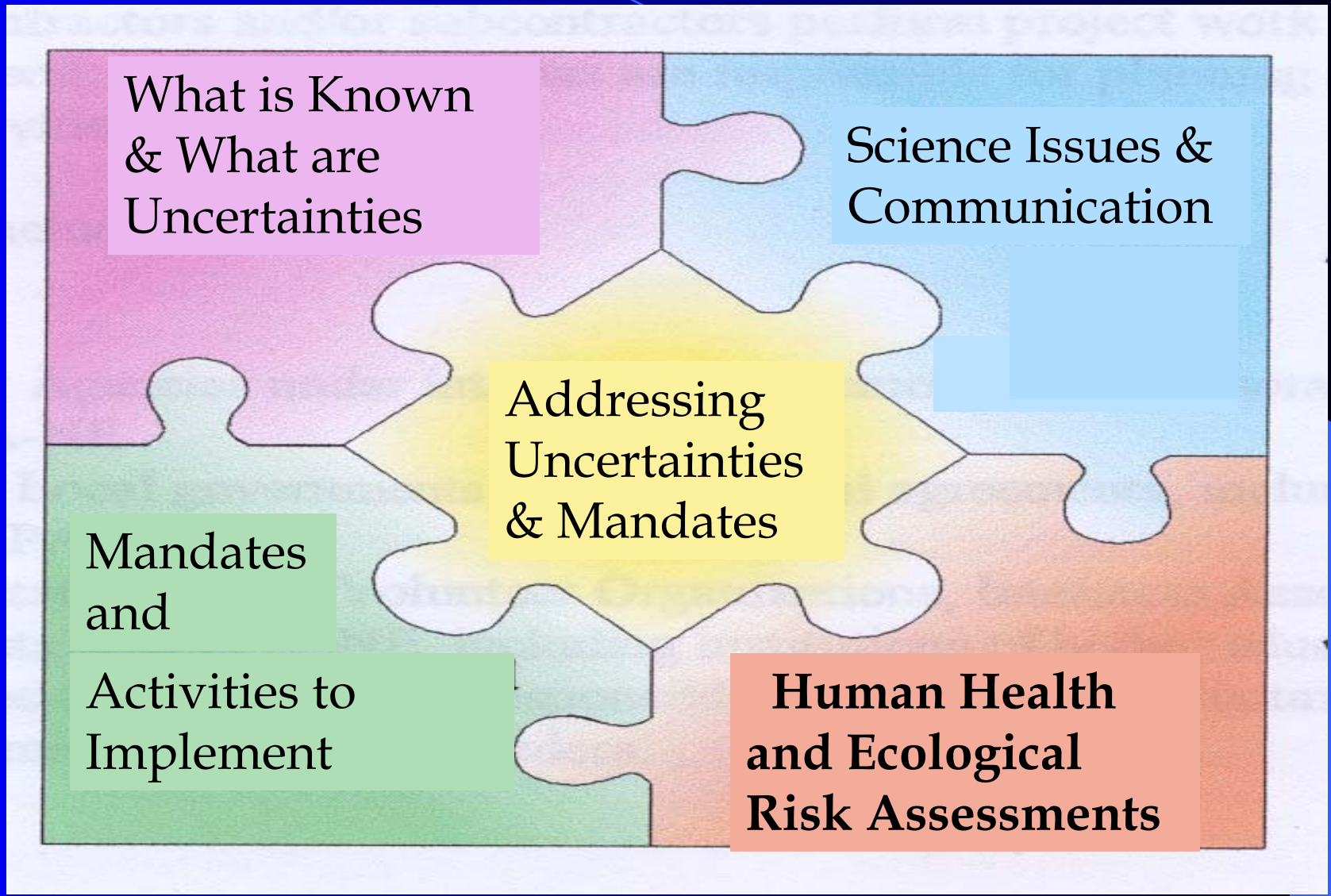
Major Uncertainties (Cont'd)

- **Chemical diversity**
  - **~100; Structures and potency; phytoestrogens**
  - **What will EDSP tell us?**
- **Multiple mechanisms of action**
  - **>1 receptor, co-factors and co-repressors**
  - **Dissimilar modes and similar phenotypes**
  - **Polymorphisms/Environmental Genome Project**
- **Cumulative exposures and effects**
- **Do EDCs need special consideration in risk assessment?**

Elements of ORD's Research Plan Based on the Risk Assessment Paradigm

- **Exposure Studies**
  - Characterization framework
  - Exposure assessment tools
  - Environmental concentrations
- **Biological Effects Studies**
  - Chemical classes and potencies
  - Dose-response relationships
  - Endocrine profiles in wildlife
  - Extrapolation to populations
  - Mixtures
- **Linkage Studies**
  - Exposures in impacted populations
  - Classes and concentrations associated with observations
  - Status and trends evaluations
  - Risk management approaches

ED Workshop Themes



ORD/NERL EDC Exposure Method Development

- **Methods Development, Refinement, and Adaptation**
  - **Methods established and published for collecting samples from soil sediment, water, for aquatic and terrestrial biota and wastewater**
  - **Unique methods established for (hog lagoon) sediment, water and wastewater**
  - **Methods established for stream sampling and runoff events (sequential automated samplers)**

ORD/NHEERL EDC Human Health Risk Information

- **PCBs**
- **Dioxins**

Nearly All Vertebrate Animals Examined Respond to Dioxin

- Humans have the Ah Receptor and the other members of its signaling complex
- Human cells and organs in culture respond to dioxins
- Biochemical responses have been measured in exposed people
- Adverse effects have been seen in highly exposed populations

Dioxin Body Burdens (ng/kg) Associated With Effects

Adverse Effects

Developmental neurotoxicity: 42

Developmental reproductive toxicity: 28-73

Developmental immunotoxicity: 50

Adult immunotoxicity: 10

Endometriosis: 42

Biochemical Effects

CYP1A1 Induction — 3

CYP1A2 Induction — 10

IL1b Induction — 10

EGF receptor downregulation — 3 stress

Functional Effects

Dioxin Non-Cancer Effects

- **Empirical Modeling**
  - **Lowest ED_{01} - 1.3-11 ng/kg**
- **Mechanistic Modeling**
  - **Range of ED_{01} - 0.17-105 ng/kg**

Dioxin Cancer Effects (Animals/Humans)

- **Linear Model**
- **Excess Risk to Background Population**
  - **~10^{-3}**
  - **Assume Mean Body Burden = 5 ng TEQ/kg**
- **Based on Analysis of Both**
  - **Liver Tumors in Female Rats**
  - **Increase in All Cancers in Exposed Workers**

ORD/NHEERL EDC
Ecologic Receptor Effects Research

- **Focus Area 1: Development & Standardization of Protocols to Identify Endocrine Disrupting Chemicals (EDCs)**
- **Focus Area 2: Developmental Exposure and Consequences**
- **Focus Area 3: Population Level Effects of EDCs in Wildlife**
- **Focus Area 4: Effect of EDCs on Development of Endocrine Diseases**
- **Focus Area 5: Inter-Species Extrapolation of the Effects of EDCs**

Endocrine Disrupting Chemical Test Protocols

- **Tier 1 Tests**
  - Receptor binding assays (ER and AR)
  - Uterotrophic
  - Hershberger
  - Pubertal female
  - Steroidogenesis
  - Frog metamorphosis
  - **Fish reproductive screen**
- **Tier 2 Tests**
  - Mammalian development and reproduction
  - Avian development and reproduction
  - **Mysid shrimp life cycle**
  - **Fish reproduction and development**
  - Amphibian development and reproduction

Why Screen EDCs with CRUSTACEA (Mysid Shrimp) ?

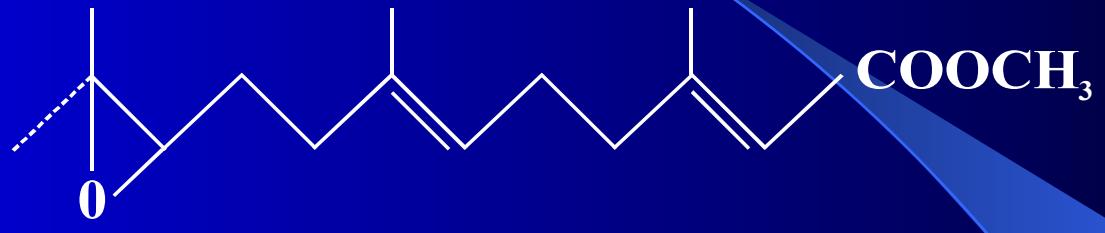
I. DOMINANT NON-TARGET AQUATIC ARTHROPOD

II. SIMILARITIES IN ENDOCRINOLOGY OF INSECTS AND CRUSTSCEA

III. ECOLOGICAL IMPORTANCE - TROPHODYNAMIC ROLE

IV. ECONOMIC IMPORTANCE

Similarity in Structure of Insect and Crustacean Hormones and a Reference Juvenile Hormone Analogue Used as Pesticide

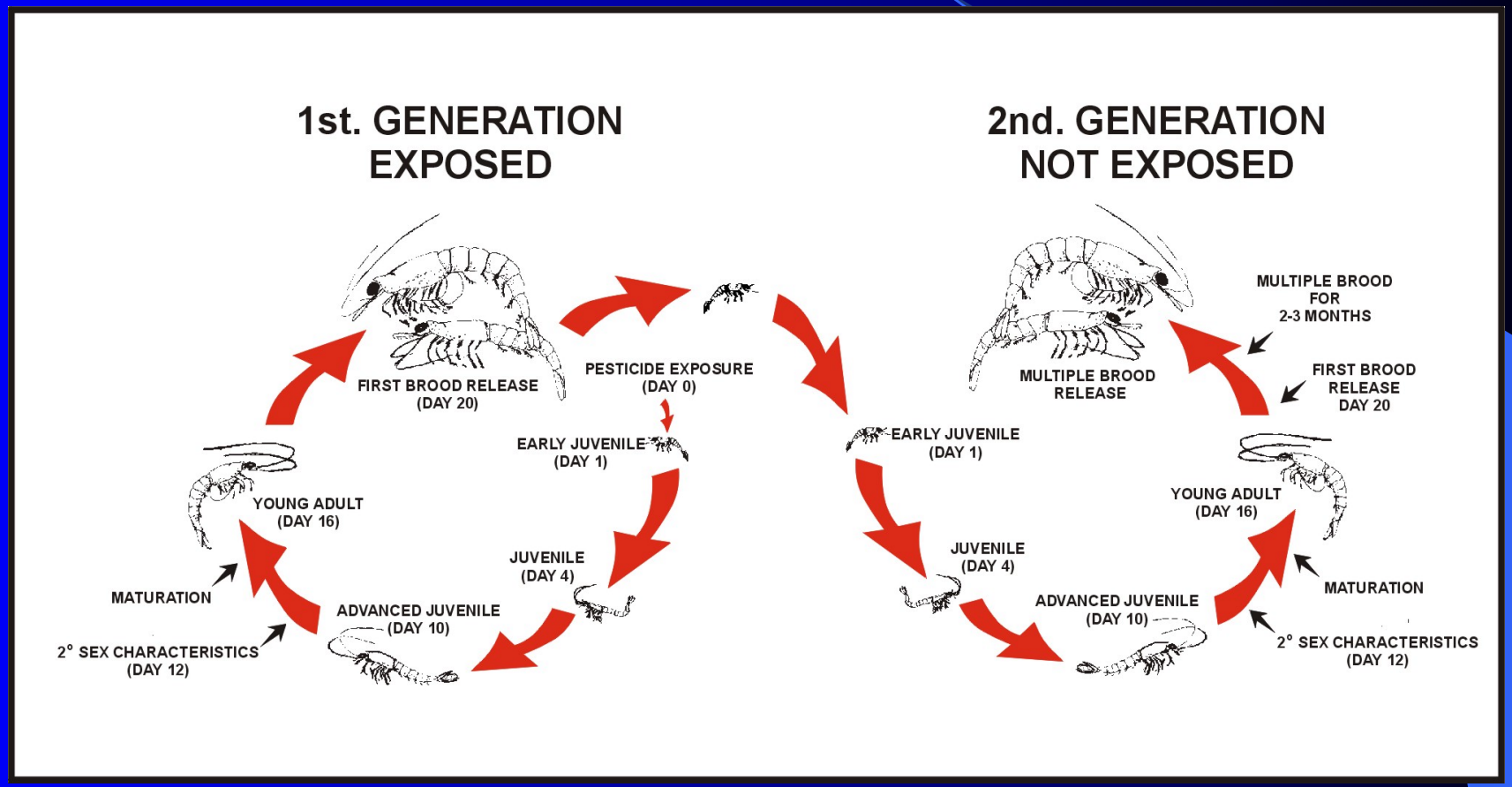


JUVENILE HORMONE

METHYL FARNESOATE

METHOPRENE
(A JUVENILE HORMONE ANALOGUE)

TRANSGENERATIONAL EFFECTS ON MYSIDS



Why Screen EDCs with FISH?

- Wide-spread effects due to EDCs could be affecting this class of animals
  - Feminization/vitellogenin production associated with municipal effluents
  - Reproductive/endocrinological effects associated with pulp/paper effluents
  - Developmental impacts in Great Lakes salmonids
- Possess unique receptors/steroids/reproductive processes potentially not captured by other proposed (Tier 1) screening assays

ORD/NHEERL Research: Bioassays for Identification of Endocrine Disrupting Chemicals in Fish

- ***In vitro*** **Bioassays & QSAR Modeling**
  - **Rainbow Trout ER Binding**
  - **Rainbow Trout Liver Vitellogenesis**
- ***In vivo*** **Bioassays**
  - **Fathead Minnow (Pimephales promelas): freshwater fish**
  - **Cunner (Tautogolabrus adspersus): estuarine fish**

In vitro Assay Systems

Advantages

- Relatively rapid & inexpensive
- Reflective of specific mechanisms/pathways of concern

Disadvantages

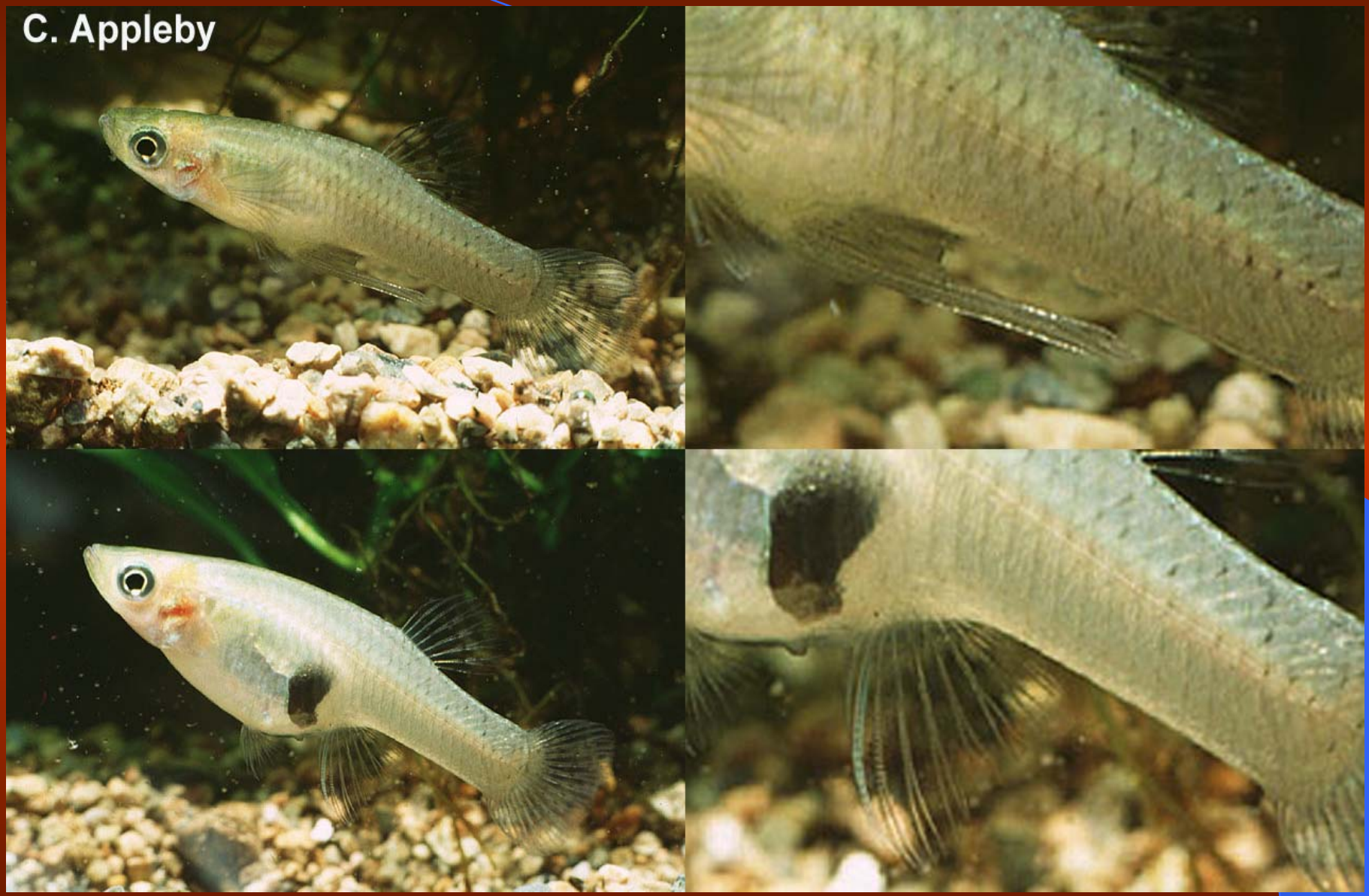
- May miss "unexpected" mechanisms
- Do not directly reflect responses on assessment endpoints of concern in Ecologic Risk Assessment (e.g., reproduction, fecundity)

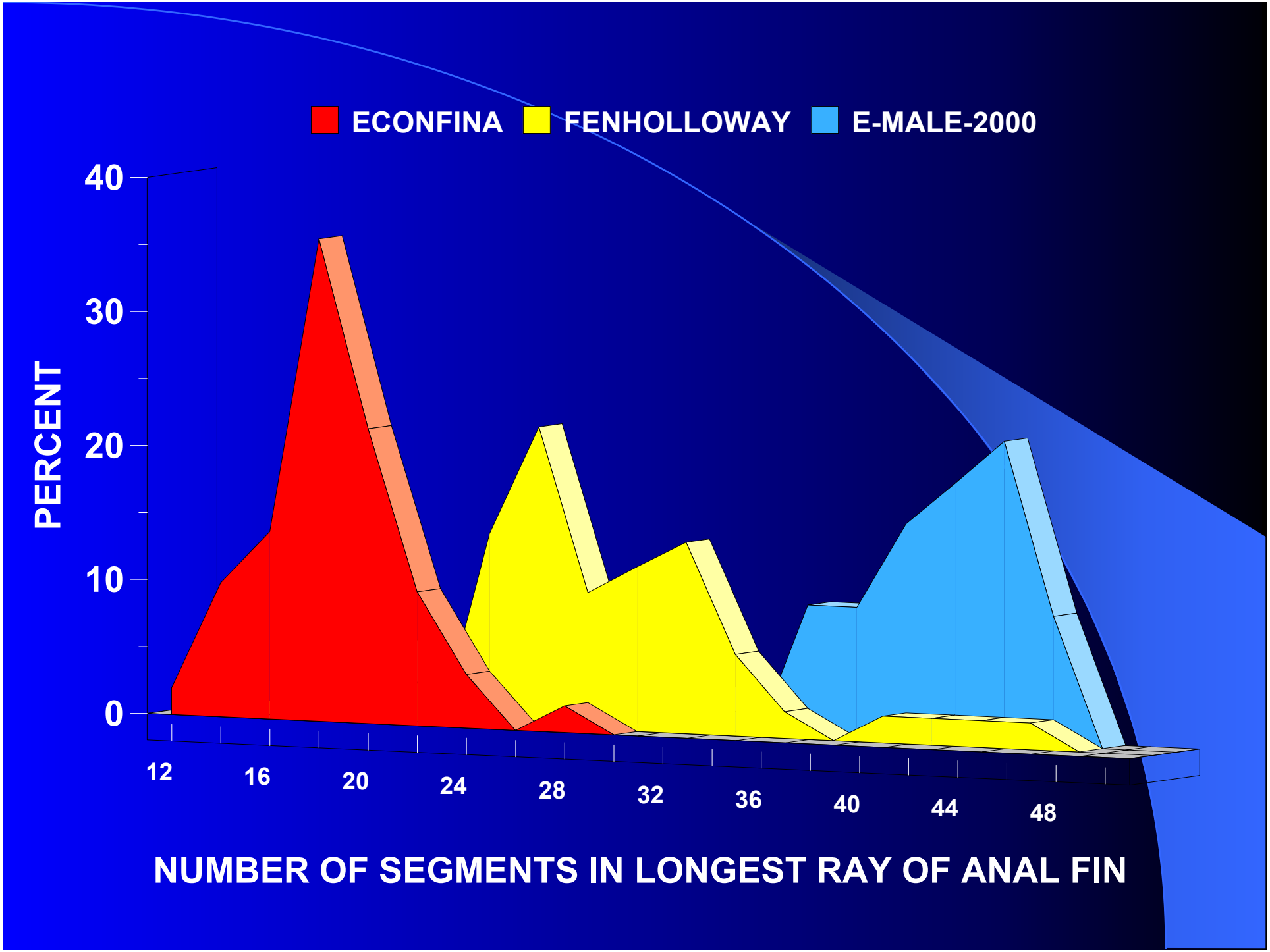
In Vitro Assays: Next Steps

- **Compare trout ER binding data base and metabolic activity with mammalian data base**
- **Develop fish-specific QSAR models for rtER binding**
- **Screen TSCA and FIFRA inventories to rank estrogenic potential & prioritize testing for fish**

In Vivo Bioassays: Applications

- **Screen for Endocrine 'Activity' - measure 'endocrine axis' endpoints (e.g., Vitellogen, hormones, secondary sex characteristics)**
  - **single chemical testing (e.g., OPPTS screening & testing)**
  - **effluents / mixtures**
    - **"in-line" testing of effluents**
    - **combine with other assays to identify chemicals responsible (TIE-like approach)**
- **Short-term Reproductive Toxicity Assay – measure fecundity endpoints (e.g., egg production, fertility, egg survival & hatch)**


C. Appleby


ECONFINA
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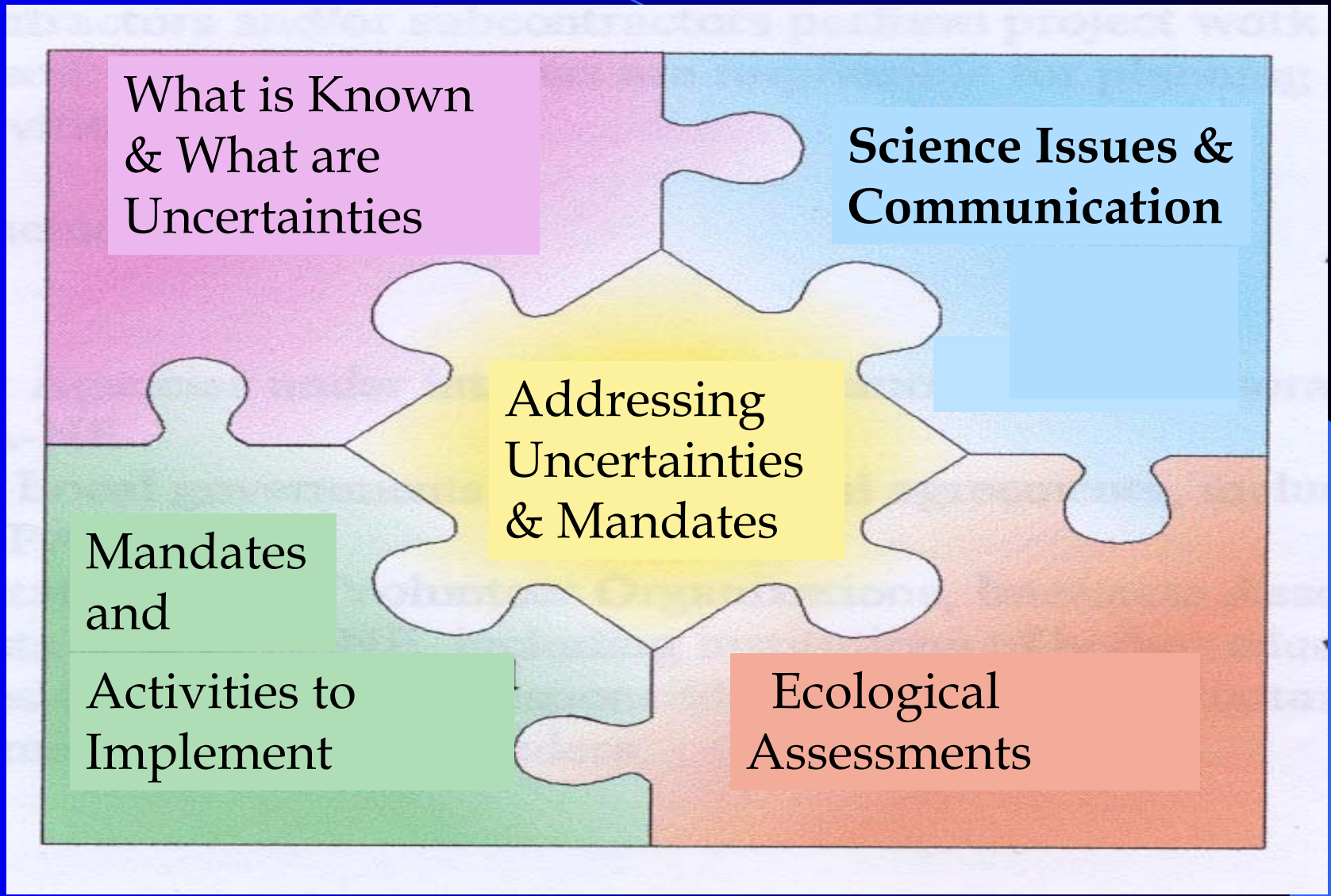
NUMBER OF SEGMENTS IN LONGEST RAY OF ANAL FIN

ED Workshop Themes



ED Workshop Science Communication Activities

- **Participants discussed how to use and communicate upcoming EDSTAC data to the scientific community and the public**
- **A mock public meeting was followed by breakout sessions to begin development of answers to frequently asked questions**

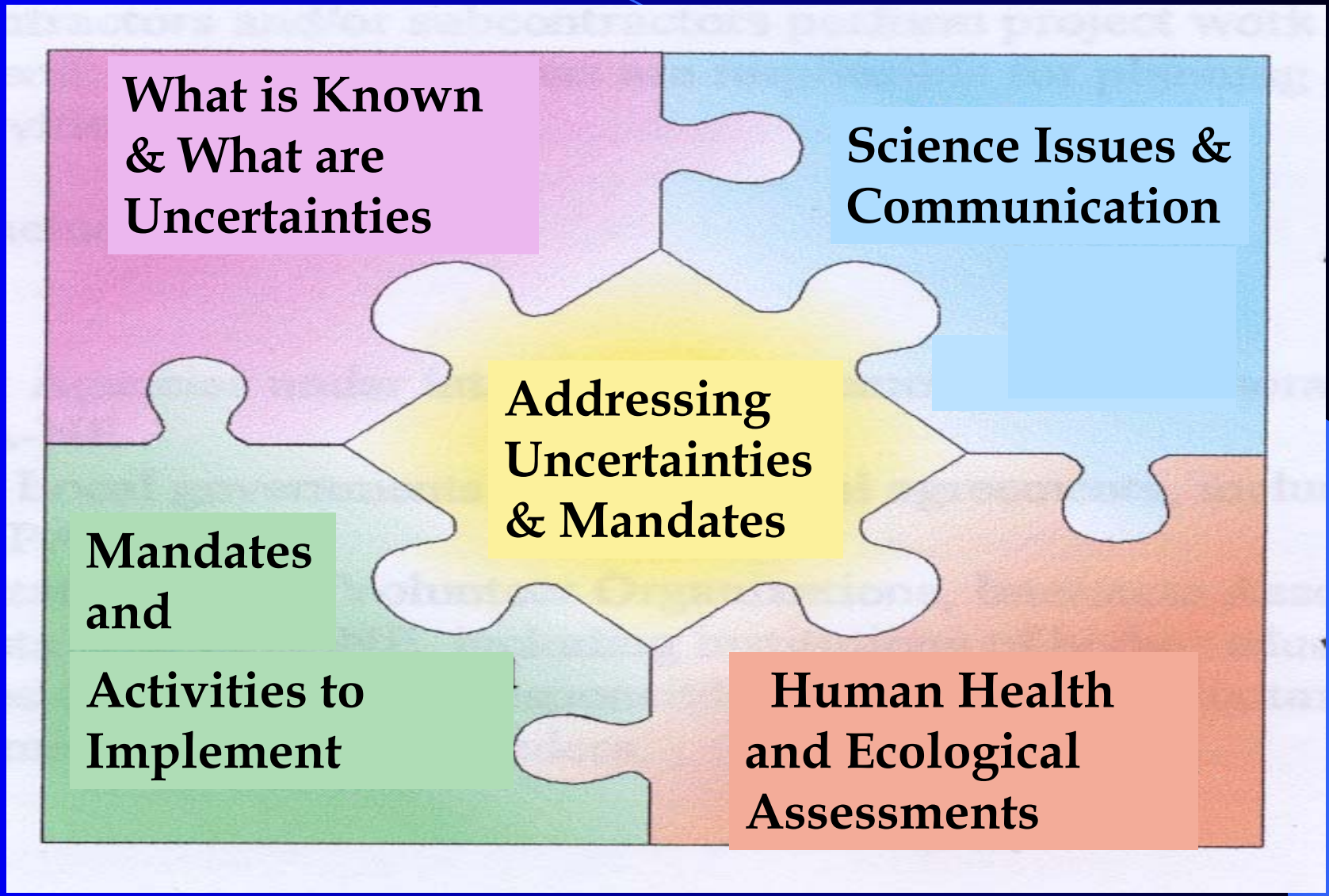
Stakeholder Concerns Regarding EDs

- **Effects of Endocrine Disruptors on thyroid and reproductive systems**
- **Impacts to children *in utero***
- **Unknown effects of EDs**
- **Differences in scientific opinion**
- **Protectiveness of clean-up goals**

Communications on Endocrine Disruptors Must Be Specifically Targeted

- **Managers**
- **Communities**
- **Responsible Parties**
- **States and Other Stakeholders**

Overview of ED Workshop Themes



Summary

- **ORD is currently validating EDSTAC testing protocols**
- **Data generated to date has not changed EPA policy/position on endocrine disruptors**
- **EDSTAC screening tests are not designed for (Superfund) risk assessment purposes**
- **Some of the ED tests being developed by ORD may be suitable for modification for use in ecologic risk assessments**

Contact Information

- **Elaine Francis (ORD/NCER - ED Research Program Manager)**
- **David Klauder (ORD/OSP - RSL Program Manager)**
- **Anthony Maciorowski (OPPTS/OSCP)**
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Contact Information

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- **Marian Olsen (Region 2)**

- **http://www.epa.gov/endocrine**

Acknowledgements

- **Elaine Francis (ORD/NCER)**
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- **Tala Henry (ORD/NHEERL-Duluth)**
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- **Gary Timm (OPPTS/OSCP)**
- **Donald Rodier (OPPTS/OPPT)**
- **Robert Kavlock (ORD/NHEERL-RTP)**
- **Charles McKenney (ORD/NHEERL-Gulf Breeze)**
- **Chuck Steen (ORD/NERL-RTP)**